REMARKS

The only issues outstanding in the office action of June 23, 2010, are the rejections under the doctrine of obviousness-type double patenting, and 35 U.S.C. 103. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Obviousness-type Double Patenting

Claims 1, 3-5 and 9-16 have been rejected under the doctrine of obviousness-type double patenting over claims 1-3 of the parent patent U.S. 6,646,007. The attached terminal disclaimer renders this issue moot, and withdrawal of this rejection is respectfully requested.

The Examiner is thanked for indicating the previous rejection under 35 U.S.C. 103 has been withdrawn.

Rejection Under 35 U.S.C. 103

Claims 1, 3-5 and 9-16 have been rejected under 35 U.S.C. 103 over Reynolds '332 taken with Mitra '105 and Remington's. This is a reformulation of the prior rejection under 35 U.S.C. 103, in which Reynolds was the primary reference. Reconsideration of this rejection is respectfully requested.

As may be recalled, Reynolds discloses a pharmaceutical composition comprising a carrier and the reaction product of tertiary phosphine with thyroxine and 3, 5, 3'-L-triiodothyronine. The Office Action admits, at page 4, that Reynolds fails to teach gelatin in the combination. There are additional significant differences between the disclosure of Reynolds and the present claims. For example, the office action cites column 7, lines 65-67 of Reynolds for the argument that "no organic solvent is present." This conclusion, however, is unfounded. The noted portion of Reynolds discloses that the "combinations used in this evaluation [of L-thyroxine and L-triiodothyronine] were prepared by physically admixing various amounts" of the compounds. Simply reciting that the compounds are in "physical admixture" means only that the compounds are physically admixed – nothing more. This disclosure does not mean, as apparently taken in the office action, that the mixture is "free of organic solvent". Moreover, it is clear that the opposite is true. Page 4 of the office action refers to composition I and J at column

7. However, the compositions are used therein to produce tablets in a process in which the ingredients are "granulated with a "alcoholic solution of polyvinylpyrrolidone." See col. 7, lines 14 and 15, 33 and 34. Thus, the materials are not "free of organic solvent." Thus, Reynolds contains several significant deficiencies verses the present claims.

Moreover, the secondary references also fail to suggest the use of gelatin "as a binder", as recited in the present claims. Mitra is cited for the proposition that "proper selection" of a binder and filler, and disintegrant, lubricant, etc. is necessary to produce a stable formulation for levothyroxine in solid dosage form. However, with regard to specific binders disclosed therein, Mitra only generically discloses that "suitable compatible" binders, disintegrant, lubricants, etc. should be used. See col. 3, lines 30-32. Indeed, such would be apparent to one of ordinary skill in the art. In fact, Mitra contains a very specific teaching as to how to improve stability of a levothyroxine preparation. Mitra teaches that stability is increased by the use of an inorganic salt, a carbohydrate having molecular weight greater than 500 or glycine, see col. 2, lines 61-67. Mitra teaches that lactose, glucose and sucrose are incompatible with their formulation, see col. 3, lines 30-31. Thus, Mitra does not suggest particular binders, much less gelatin.

It is further important to realize that Mitra does not teach avoidance of lactose, glucose, sucrose etc. as *binders* with thryoxine, but refers to them only as fillers. Note that Mitra describes these "excipients" as "bulker or diluent", thus clearly a filler, not a binder.

With respect to the difference between fillers and binders, it is apparent that there is perhaps a misunderstanding in the office action. It is well known to those of ordinary skill in the formulation art that the function of auxiliaries in a pharmaceutical formulation depend on the composition as well as the process of manufacture. If, for example, a concentrated sugar solution (i.e. a syrup) is mixed with other ingredients and subsequently dried, it will form a crust. Within such a crust sugar has a binding function so that it can be called, within the limits of such a formulation, a binder. However, if the sugar is used in a dry form and if it is compressed to a tablet, such sugar does not execute a binding activity but acts as a filler, i.e., the sugar does little or nothing to hold the tablet together. The same applies to starch, which together with water can form a starch paste and, if mixed with other auxiliaries and dried, may have a binding function. If starch is used within a formulation as a dry powder, however, the starch has no binding activity and its function is again that of a filler. By contrast, where gelatin is used as an aqueous solution

leading to formulation, it functions as a binder, holding the tablet together.

The formulation of the present examples contain a sugar, starch, gelatin, levothryxoine sodium as the active ingredient and magnesium stearate as a lubricant. If there were no difference between binders and fillers, as apparently they are used interchangeably in the office action, then the tablet of the present invention would besides the active ingredient and the lubricant contain only binders. This would not make any sense.

In fact, one of ordinary skill in the art would see that in the formulation of the present invention maize starch and lactose monohydrate act as fillers, whereas gelatin has the function of a binder. This is because only gelatin is dissolved and used as a solution (wherein levothyroxine is suspended).

Thus, Mitra does not eliminate lactose, glucose, sucrose etc. as binders, but as bulkers or fillers. Mitra teaches different binders than these materials, including microcrystalline cellulose, maltodextrin, starch and hyroxpropyl cellulose, see col. 4, lines 12-14. Gelatin is not mentioned. As a result, one of ordinary skill in the art is not left with a choice between only starch and gelatin where levothryoxine is concerned, even considering the well known disclosure of Remington. In fact, a large number of binders are known in the pharmaceutical field. Attention is directed to the attached excerpt from the pharmaceutical dictionary Hunnius Pharmazeutisches Worterbuch. "The Hunnius" is the standard dictionary in the pharmaceutical field, it is present in nearly every German-language pharmaceutical library, pharmacy and pharmaceutical laboratory. As clearly set forth herein under "Bindemittel" (which means binders): *"Als B. warden verwendet: Zucker, Starken, Gelatine, Cellulosederivate, Gummi arabicum, Tragant, PEGs, PVP u.v.a"* meaning *As binders are used: sugars, starches, gelatin, cellulose derivatives,gummi arabicum, traganth, polyethylene glycols, polyvinyl pyrrolidone* and many others. A multitude of different binders exist, from which the binder has to be selected.

It is again respectfully maintained that the two declarations of record further establish the non-obviousness, and thus patentability, of the present claims. In the first Declaration, comparison is made between a formulation containing gelatin, and one containing the polymer HPMC, (hydroxypropylmethylcellulose). The declaration shows that, unexpectedly, where gelatin is substituted for HPMC as a binder, active agent content over time is significantly greater for compositions formulated with gelatin then the active agent content maintained for those

formulated with HPMC. One of ordinary skill in the art would not expect such a beneficial and significant stability effect for gelatin, as nowhere in the cited references is any advantage taught for gelatin; gelatin is simply one of many possible fillers or binders. In the second Declaration it is shown that a formulation according to the invention, which contains a small amount (2.50 mg) of gelatin as binder has a better stability than the same formulation containing 3.50 mg HPMC, which is the most frequently used binder. The improvement of stability further increases with the amount of gelatin in a dose-dependent way.

It is accordingly respectfully maintained that the declarations show unexpected results.

Accordingly, withdrawal of all of the rejections is again respectfully requested.

The claims of the application are submitted to be in condition for allowance. However, if the Examiner has any questions or comments, she is cordially invited to telephone the undersigned at the number below.

It is finally noted that the present office action indicates that claims directed to the specific formulations of the example would be given favorable consideration. Such claims have been added as new claims 17 and 18.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Harry B. Shubin/

Harry B. Shubin, Reg. No. 32,004
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: MERCK-2168-D1

Date: September 23, 2010